Matrix Metalloproteinases in Atrial Fibrillation

We read with great interest the study by Boixel et al. (1), which examines the importance of matrix metalloproteinase (MMP) system in atrial remodeling in a rat model of heart failure. The investigators demonstrate the up-regulation of MMP-2 and MMP-9 in the atria with marked structural abnormalities, but there were no significant differences in tissue inhibitors of MMP (TIMP) activity.

The clinical significance of the report by Boixel et al. (1) requires clarification in a (human) patient population. We recently explored plasma levels of MMP-1 and TIMP-1 in 48 consecutive patients with chronic nonrheumatic atrial fibrillation (AF) (2) and found evidence of impaired matrix degradation, with lower levels of MMP-1 and increased levels of TIMP-1 compared with controls. However, these values were not *independently* associated with the presence of AF on multivariate analysis. Instead, clinical (i.e., age, ischemic heart disease, or hypertension) and echocardiographic variables (end-diastolic left ventricular diameter or left ventricular mass index) were found to be independently associated with MMPs. In a preliminary study, decreased MMP-1 activity was found in the atria of AF patients undergoing open-heart surgery (3).

There are controversial data whether structural changes in the atria are related to AF (4,5) or to underlying diseases (6,7). Our findings (2) and those of Boixel et al. (1) suggest that increased interstitial fibrosis in atrial tissue is more likely due to underlying comorbidities, like hypertension, ischemic heart disease, or uncontrolled heart failure (circumstances associated with high risk to develop AF), than to the presence of arrhythmia itself. Moreover, experimental data suggest that underlying diseases promote AF by causing atrial interstitial fibrosis (8). Certainly, decreased concentration of MMP-1 (the most important enzyme in the extracellular degradation of collagen types I and III) with raised levels of TIMP-1 have been observed in hypertensive patients (9). In this setting, TIMP-1 has been recently proposed as a noninvasive marker of fibrosis in a large cohort of untreated hypertensive subjects (10).

Finally, the possible relationship of the MMP system to the thromboembolic risk in AF merits exploration. For example, an independent relationship was observed between the MMP system and the prothrombotic state in AF (as assessed by prothrombin fragment 1 + 2 levels) (2).

Francisco Marín, MD, PhD
Vanessa Roldán, MD, PhD
Vicente Climent, MD
Gregory Y.H. Lip, MD, FACC, FESC
University Department of Medicine
City Hospital
Birmingham B18 7QH
United Kingdom
E-mail: g.y.h.lip@bham.ac.uk

doi:10.1016/j.jacc.2003.10.019

REFERENCES

1. Boixel C, Fontaine V, Rücker-Martin C, et al. Fibrosis of the left atria during progression of heart failure is associated with increased matrix metalloproteinases in the rat. J Am Coll Cardiol 2003;42:336–44.
2. Marín F, Roldán V, Climent V, García A, Marco P, Lip GYH. Is thrombogenesis in atrial fibrillation related to matrix metalloproteinase-1 and its inhibitor, TIMP-1? Stroke 2003;34:1181–6.
3. Goette A, Nepple K, Arndt M, et al. Atrial expression of matrix-metalloproteinases in fibrillating human atria (abstr). Eur Heart J 2003;23 Suppl:138.
4. Ausma J, Wijffels M, Thone F, Wouters L, Allessie M, Borgers M. Structural changes of atrial fibrillation due to sustained atrial fibrillation. Circulation 1997;96:3157–63.
5. Frustaci A, Chimenti C, Bellocci F, Morgante E, Russo MA, Maseri A. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. Circulation 1997;96:1180–4.
6. Schotten U, Ausma J, Stellbrink C, et al. Cellular mechanisms of depressed atrial contractility in patients with chronic atrial fibrillation. Circulation 2001;103:691–8.
7. Shirani J, Aleddini J. Structural remodeling of the atrial appendage in patients with chronic non-valvular atrial fibrillation: implications for thrombus formation, systemic embolism, and assessment by transesophageal echocardiography. Cardiovasc Pathol 2000;9:95–101.
8. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs. Atrial remodeling of a different sort. Circulation 1999;100:87–95.
9. Laviades C, Varon N, Fernández J, et al. Abnormalities of the extracellular degradation of collagen type I in essential hypertension. Circulation 1998;97:1708–15.
10. Lindsay MM, Maxwell P, Dunn FG. A marker of left ventricular diastolic dysfunction and fibrosis in hypertension. Hypertension 2002; 40:136–41.

REPLY

Marín and collaborators report that, in patients in atrial fibrillation (AF), plasma level of MMP-1 is decreased while that of TIMP-1 is increased, suggesting an impaired matrix degradation in this clinical setting (1). Because alteration in the MMP/TIMP system correlates with left ventricular mass and remodeling but not with AF, the investigators conclude that the atrial fibrosis is caused by the underlying diseases. This is in agreement with our studies in a rat model of heart failure with atrial dilation (2) or in human right appendages (3) showing that structural alterations of the atrial myocardium are associated with left ventricle dysfunction, independently of AF.

An apparent controversy exists between the decreased MMP-1 and increased TIMP-1 in plasma of patients in AF (1) and the up-regulation of MMP-2 and MMP-7 (and not MMP-9 see the letter of Marín et al) but not of TIMPs in our model (2). One explanation is probably that we studied protease activity in tissue and not in plasma. This point is crucial for MMP-7, which is anchored to cell basement membrane, thus preventing its diffusion and probably any increase in the plasma (4).

Myocardial fibrosis is a dynamic process during which normal collagen chains are degraded and replaced by fibrous interstitial deposits. The MMPs are involved both in matrix degradation and collagen synthesis (5). Thus, their up-regulation in dilated rat atria suggests an ongoing activation of processes leading to matrix remodeling. This may not be the case in patients with long-lasting history of AF and a therapeutically controlled hypertension or heart failure (1). A time-dependent MMP activation is well known during the progression of cardiopathies. Acute pressure overload induces myocardial MMP activation that normalizes with the prolongation of the pressure overload (6). Distinct regulations of